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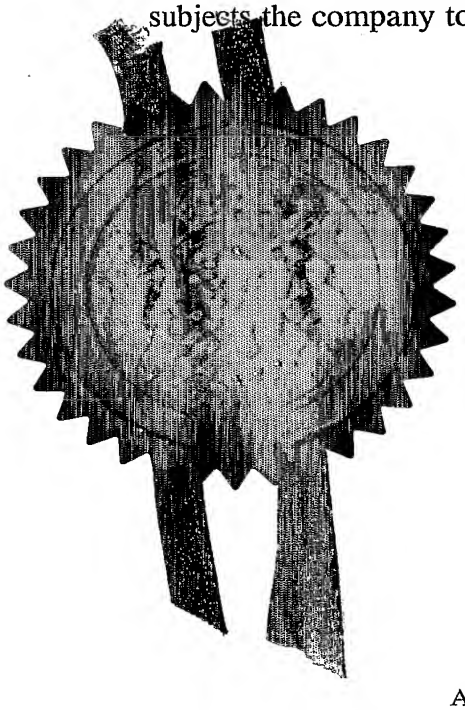

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Patents ADP number *(if you know it)*

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4. Title of the invention

NMR LEAK TEST

5. Name of your agent *(if you have one)*

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Signature(s) S D Hoath Date 22nd Dec 2003

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NMR LEAK TEST

Field of the invention

This invention relates to methods of testing integrity of a fluid container, test equipment for validating inhaler integrity, and inhaler products validated by these methods or equipment.

Background to the Invention

It is known to test the integrity of fluid containers in applications such as production line validation of filled inhaler devices such as metered dose inhalers.

Validating the integrity of pressurised devices such as metered dose inhalers (MDIs), is harder if they are filled with fluorine containing propellants such as R134a or R227 (FM200) that are relatively quite hard to detect compared with the previous generation of (CFC) propellants that were used in MDIs.

The propellants are usually contained in liquid and gas phases within pressurised MDIs (pMDIs), and any defects in the containment allow gas and liquid propellant losses. The typical quality of pMDI production is better than 1 defective in 1 million devices, but should a pMDI lose too much propellant prior to usage before the "best by date", the pMDI device will not be able to deliver the expected quantity of drugs to a user. Therefore methods are stipulated for every pMDI that is shipped for use by consumers.

The sensitivity required is specified by the regulatory bodies and agencies such as the American Food & Drug Administration (FDA) is about 0.5g/year of HFA propellant, which translates to typical leakage rate of $4x10^{14}$ molecules per second or $2x10^{-5}$ mbarl/s at 21°C. These levels are themselves challenging for MDI production lines due to the speed of the filling processes and the accidental

releases of propellant that inevitably occur nearby, and greatly reduced chemical activity of the CFC-replacement propellants.

Existing methods used for this purpose comprise either weighing the whole MDI after filling with the propellant at intervals of typically a week to 10 days or attempting to measure the gases lost with chemical sniffers or quadrupole analysers in production. Physical methods are better for propellants but conventionally require very fast readout of the measurement because of the speed of production, typically 100-200 MDIs per minute.

Grossly leaking MDIs, which lose propellant at high rates, are readily and usefully detected by simple means, but the validation to high sensitivity levels requires better techniques.

Accumulation chambers for the collection of leaking gases or liquids are used to help enhance the sensitivity of the methods used or proposed by the present author (see for example GB2376748, GB2376749 and GB2376750) for production line testing. Such chambers allow for background by either pre-evacuation or signal subtraction methods, which may be in electronics or in software or a combination of the two approaches.

These accumulation chambers are either conventionally and permanently mounted on rotary table or indexing machines, and therefore have to be read out within the cycle time of the machine (within seconds) or, as proposed by the present author (see for example GB2376749 and GB2376750), loaded onto the production line itself with either cheap integral leak sensors on each chamber or a more expensive off-loading chamber reading station which effectively measures gases accumulated for a long time (in minutes) downstream of the chamber loading machine.

NMR techniques are widely used with solid and liquid samples, but not with gases, because of the significant reduction of sensitivity and contrast available. In addition, the vast majority of NMR applications are used for scanning and

imaging in medical or oil surveying and are based on proton detection not 19F detection, which is otherwise very similar in principle. There are however some specific non-scanning 19F NMR devices.

Small-bore NMR analysis systems have a vertical magnet well to take a sample of solid or liquid material. The sample is weighed and placed in a tube then lowered into the well to determine the level of 19F present in the sample.

For the level of 25ppm detected to 20% precision, the manufacturers of a 19F NMR analyser type MQA7019 by Oxford Analytical Instruments, UK have provided some analysis time estimates of 10 minutes, which might be reduced a bit by use of paramagnetic salts mixed with normal samples such as toothpastes and fluorine bearing minerals. Since, typically, the required HFA test time in a production test system is about 1 second, use of conventional and available 19F NMR techniques appears to be limited to laboratory testing.

Summary of the Invention

An object of the present invention is to provide improved apparatus or methods.

A first aspect of the invention provides a method of testing integrity of a fluid container using NMR analysis.

The detection of leakage using NMR analysis is non-destructive and based on physical principles rather than chemical conversion or by signal suppression. Other techniques disrupt fluid molecules either physically or chemically or are physical tests that are still non-selective for the contents of the fluid container.

NMR analysis is hitherto commonly used in medical or oilfield imaging, but it is not necessary to provide imaging NMR systems to detect fluid leakage, so that suitable analysis systems are far less expensive and elaborate than these and use can now be envisaged for more routine applications in industry.

NMR is also used for quantitative analysis of some atomic concentrations in minerals and products, but it is not necessary for the application to detect fluid leakage to provide NMR analysis systems having a vertical well geometry for the magnetic bore of the NMR analyser system: side entry NMR systems should be easier to integrate with normal production lines and sample flow through configurations can be considered. There have not been prior suggestions for use of NMR techniques for fluid container integrity testing by fluid leak detection, nor prior suggestions for use of 19F NMR applied to pMDI inhaler integrity validation, nor for the validated inhaler products following use of the proposed methods or the equipment.

The method of testing can be part of a method of making the product, or part of a method of using the product. The testing could be carried out in the industrial production of the product or as part of or following use of the product in the field.

In the method as set out above, as an additional feature, the fluid container may comprise an inhaler, and the testing comprise testing for leakage of propellant from the inhaler.

The inhaler contains propellants that are difficult and or expensive to reliably detect directly by other methods already used or proposed for testing integrity.

Testing for leakage of propellant from an inhaler using NMR analysis can be directly related to the validation of dispenser integrity sought by the FDA rules and requirements for the production of highest quality metered dose inhalers.

The method as set out above may have a step of accumulating propellant leakage in a chamber.

An accumulation step increases the number of propellant molecules or atoms available for detection, usually in proportion to the length of the period used for accumulation, thereby increasing the test sample quantity to be analysed and providing a faster analysis for validation by detection of low-level leakage.

In conventional NMR systems, the sample composition is fixed and a known weight of it is dispensed into a sample tube or similar. In the proposed method an accumulation step permits the content of the sample to change over time.

In some embodiments this can enable NMR analyses to be applied before, during and or after such accumulation, to ensure that the accumulation can be determined and assigned to leakage.

The fluid container under test is not usually moved with its own accumulation chamber right into the NMR analyser bore: for inhalers they could be moved together, although practice this is unlikely and is impractical for larger vessels.

In the method as set out above an inhaler may contain fluorinated compounds and the NMR analysis involves detecting fluorine atoms in such compounds.

The inhaler propellants commonly used usually contain several fluorine atoms in each molecule, which enhances the sensitivity of the integrity testing when the NMR analysis involves detecting fluorine. Other methods are generally sensitive to the number of molecules, not atoms, of a particular component of leakage, or not specific to the containment of the propellant but to the inhaler.

In the method with accumulation as set out above some part or all of the accumulation chamber may be subsequently moved into the NMR analyser.

Since the accumulation chamber may be much smaller than the NMR analyser system or sited some way away from it, it will often be expedient to move the accumulation chamber partly or wholly into the NMR analyser system after a suitable accumulation period.

In the method with accumulation as set out above transferring the accumulated chamber contents into a second container for analysis, which is itself then moved into the NMR analyser system.

The NMR analyser system is usually far too big, and with an external magnetic "fringing" field surrounding the NMR magnet especially near the bore such that magnetic materials of construction of the accumulation chamber also have to be kept away from it, so use of a second container for analysis is significant in avoiding this magnetic disturbance which might thereby compromise or reduce the sensitivity of the NMR analysis system.

Some particular advantages of using containers for analysis is that these can be manufactured to optimise their fit and material content (both magnetic and to minimise background signal) within the NMR analysis system without the constraints placed on the shape and size of the accumulation chamber to fit around the container being integrity validated inside. They can be smaller and be handled and transferred far more readily. The second containers can optionally be pre evacuated to reduce contamination risk for example.

In the method with accumulation as set out above multiple numbers of these containers or accumulation chambers may be NMR analysed simultaneously.

Again with the possibility of having containers for analysis that are not only shaped and constructed with appropriate materials for the NMR analysis system and of smaller size than accumulation chambers for all products, it may be advantageous to test accumulated leakages from different containers simultaneously by loading the second chambers (or accumulation chambers) into the NMR analysis system together. It may be possible to transfer these containers stepwise through the bore of the NMR analyser system as each untested container for analysis or accumulation chamber becomes available, where the size of the container or accumulation chamber and the bore of the NMR analysis system is so constructed to enable such items to pass through.

The methods as set out above may have the step of cooling the leakage.

By cooling the leakage from fluid containers, the leakage material volume can preferentially reach and remain in locations near to the NMR analysis section.

This may thereby enhance the proportion of molecules in the NMR analyser and improve the leak detection sensitivity.

This is particularly useful for condensable fluids because materials analysis by NMR methods is normally performed in solid state or liquid, not vapour states, and most significantly for low levels of fluid leakage where condensation does not occur or is physically unlikely at low concentrations outside the container.

The methods set out above may have the step of accumulating leakage on a cooled surface and measuring the amount accumulated.

An advantage of making measurements on the accumulating leakage on a cooled surface is that the amount accumulated can be compared with a pre-determined threshold value, which signifies a non-compliant level of leakage.

Another advantage is that the actual leakage rate of a fluid container can be determined to low very level by continuing the cooled leakage accumulation, which may be helpful in the establishment of the actual production margins for a batch or a particular design of container against any applicable standards.

The method as set out above and including cooling may have the step of moving the cooled surface relative to an NMR analysis system, to carry out the measurement after a period of accumulation.

The significance of this is that there may be many containers to be tested by one or just a few NMR analysers, said containers being produced in such number or at a high rate needing a significant number of accumulation chambers each fitted with cooled surface(s) moved appropriately into and out of the analyser.

The method as set out above including the accumulation of leakage may have the step of evacuating the accumulation chamber.

An advantage of evacuation of the accumulation chamber is the removal or reduction of surface spills, valve leakage or background contamination prior to starting the accumulation period. The evacuation means provided might incorporate detectors that are based on chemical detection of gross propellant leaks, so that the control of the inhaler filling, valve crimping and or background levels can be alerted to poor conditions independently of an NMR analysis.

Another advantage of pre-evacuation is the likely faster migration of the propellant molecules through the leak path and around the inhaler body placed inside the accumulation chamber.

Yet another advantage of pre-evacuation may be enhancement of the propellant leakage rate through any defects in the inhaler container.

A second aspect of the invention provides test equipment means for validating inhaler integrity using a NMR analysis system for analysis of propellant leakage accumulated within a chamber.

Provision of such test equipment significantly improves the basis for validation of containers such as metered dose inhalers over high-speed weight checkers that have to be used to compare the weight of such products at different dates and eliminates or significantly reduces the warehousing requirements needed.

The test equipment as set out above may be applied where the propellant contains at least one fluorine compound and the NMR analysis is for 19F nuclei contained within the propellant molecules.

Since HFA propellants have been replacing the CFC propellants, the common chemically based CFC leak detection products have had much less sensitivity and great difficulty in providing validated products. HFA molecules all contain fluorine atoms, each of which has 19F nucleus available for 19F NMR analysis, and there is a significant %F by weight in common HFA molecules, so that the test equipment is favourable to the detection of HFA propellant leakage.

Since CFC products also contain fluorine atoms they are also favourably detected by the test equipment, with the advantage that the test equipment can handle integrity validation for CFC and HFA filled MDIs without added difficulty.

The test equipment as set out above may have a cooled surface and means for transferring accumulated propellant leakage to the NMR analysis system.

The cooled surface helps accumulation of propellant in a location or on a surface that is suitable for transfer to the NMR analysis system. The means for transferring accumulated propellant leakage to the NMR analysis system only need transfer a part of the accumulation chamber rather than both the chamber and the container under test, and therefore provides the advantage that this part is only a fraction of the size and weight of the accumulation chamber: this may be incorporated into a small bore NMR analysis system, which itself will be smaller and more economic to provide and fit into production facilities.

The transfer means may include an intermediate container that transfers the accumulated propellant leakage (with or without cooling in the accumulation chamber) into another chamber (with or without cooling surface) more suitable for insertion into the NMR analysis system. Such an intermediate container may be combined with others, to provide a simultaneous assessment means when integrity test throughput is demanding and the testing sensitivity is proven adequate.

The test equipment as set out above may have means for pre evacuating the accumulation chamber.

The pre-evacuation means permits the elimination or reduction of room background and or surface contamination of the fluid container prior to the subsequent accumulation period in order to avoid attributing these to leakage from the fluid containers. This room background or surface contamination is quite likely to occur during earlier production steps for the fluid filled containers.

The test equipment as set out above may have a cooling means comprising a Peltier effect device.

Peltier or thermo-electric devices do not require the use of cryogenic fluids, thereby providing a convenient cooling means for the test equipment to enhance the NMR signal and or help localise the accumulated propellant. Other cooling means, for example a heat pipe, may also be used to transfer heat from the cooling surface to the Peltier-effect or thermo-electric device.

The test equipment as set out above may be constructed using a material for the chamber to provide a calibration means for the NMR analysis system.

It is a significant advantage to incorporate a material within or made part of the chamber designed to have material providing an NMR reference signal that can be detected as a means of proving test equipment sensitivity with every test, which thereby enhances the reliability of the integrity validation.

Alternatively, a known special chamber with material providing such calibration means can be introduced into the NMR analysis system to demonstrate the test equipment sensitivity as required, or regularly, to establish such testing.

The test equipment as set out above may provide a means for cross checking integrity validation with an off-line NMR analysis system.

This system can be run in parallel with the normal NMR system for checking product on a batch basis or after a hiatus in the normal production testing.

By ensuring that the off-line testing can also handle the accumulated products normally tested by the on-line test system, different measurement periods can be employed in the off-line NMR analysis system in order to establish the actual leakage, surface contamination or room backgrounds with advantage.

The provision of a compatible NMR analysis system also provides an economic means of increasing throughput or minimising downtime, although since the NMR system itself need have no moving parts or cryogenic cooling for the NMR magnet field generation means (since this is not necessary in the application) this is less significant.

A third aspect of the invention provides an inhaler product validated by any of the methods or test equipment as set out above.

The validation of an inhaler product by any of the methods or test equipment as set out above confers a high level of integrity both for the inhaler and also its production, thereby meeting requirements of the FDA or other regulatory bodies for the demonstration of the required performance of every container used for inhaler products and also for production means of inhaler products.

An inhaler product could be given a mark to show it has been validated by any of the methods or test equipment as set out above.

A considerable advantage of marking an inhaler product that has been validated by the method or equipment is that the value of the product to the user and producer is enhanced by openly showing that it has been directly assessed by NMR techniques, which link to the well-respected, publicly known and high valued MRI (medical resonance imaging) techniques.

The inhaler product that is validated by any of the methods or test equipment as set out above, could have the validation mark on packaging of the inhaler product.

Likewise another advantage of marking the packaging of an inhaler product so validated by the method or equipment is that it conveys an association of high value inhaler products with publicly known MRI techniques and results, justified because the method or equipment used is based on NMR analysis.

While the purpose of the invention is on-line integrity testing of containers, for CFC-replacement propellants such as used within pMDIs, that are generally hand-held cans having overall dimensions of a few centimetres or inches, it is clear that other fluid container integrity applications could adopt the approach.

All devices containing fluorinated compounds are testable using this method, though the test equipment will be far bigger and slower for fire extinguishers using FM200 than for R227 pMDI testing machines, even though FM200 is the same compound as R227. Other fluorinated compounds used extensively by industry, including SF_6 used in high voltage switchgear, could be detected.

Industrial devices containing SF_6 are not moveable, so the application of the invention to them most likely requires transportable fluorine NMR analysis and transfer system with an accumulation chamber partially covering the product. Heavier-than-air insulating gas from a leaking product might be accumulated in hoods surrounding all high voltage and pump feed-through parts of an SF_6 switchgear held on suitable lifting gear well above the leak testing system and allowed to flow by gravity into a vertical well fluorine NMR analysis system.

Other advantages will be apparent to those skilled in the art, particularly over any other prior art not yet known to the inventor. The additional features can be combined with each other and with any of the aspects as would be apparent to those skilled in the art.

Brief description of the drawings

Embodiments of the invention will now be described to show by way of example how it can be implemented, with reference to the figures in which:

Figure 1 shows some principal features of an embodiment using NMR analysis.

Figure 2 shows some principal features of another embodiment.

Figure 3 shows some principal features of another embodiment involving an inhaler and an accumulation chamber.

Figure 4 shows some principal features of another embodiment involving an inhaler with a fluorinated propellant and an accumulation chamber.

Figure 5 shows some principal features of another embodiment with the steps of accumulation 60 prior to transfer step 70 prior to the NMR analysis.

Figure 6 shows some principal features of another embodiment with the steps of pre-evacuation 30, stabilisation 110 and cooled accumulation 100 prior to transfer step 90 into a second container for analysis step 80.

Figure 7 shows some principal features of another embodiment with the steps of introducing a calibration chamber 105, loading an inhaler step 65, accumulation step 60, transfer step 70, NMR analysis step 20, post test transfer step 75 and off-line NMR analysis step 25.

Figure 8 shows some principal features of an embodiment of the test equipment with a cooled endplate 102 forming one wall of the accumulation chamber 6 and also an NMR analysis system 222 having another endplate 101 from an earlier test shown enclosed by lid 78 within tube 441 in sample well of magnet 4.

Figure 9 shows some principal features of another embodiment of the test equipment with inhalers 32 held within accumulation chambers 6 above endplates 102 mounted on pallets 170 moved by a production line transfer means 150.

Figure 10 shows some principal features of another embodiment that validates or rejects an inhaler product by the method or test equipment using NMR.

Detailed description of the Drawings

Figure 1 shows a fluid container 1 containing fluid 11 and an NMR analyser means 2 used for integrity testing of the fluid container 1. The pipe 40 connects to the sample well in the bore of the magnet 4 within the NMR analysis system 2. This analysis system also has a power supply PS and a radio-frequency RF section as used for any NMR technique.

Figure 2 shows a fluid container means that is an inhaler 3 and an NMR means 22 used for integrity testing of the inhaler by detection of the propellant fluid 5 leaking from the inhaler 3

Figure 3 shows a fluid container means that is an inhaler 3 placed within an accumulation chamber means 6 such that NMR means 22 used for integrity testing of the inhaler detects the accumulation 55 of the propellant fluid 5 leaking from the inhaler 3

Figure 4 shows a fluid container means that is an inhaler 32 containing fluorine compounds placed within an accumulation chamber means 6 such that NMR means 222 that is sensitive to fluorine is used for integrity testing of the inhaler detects the accumulation 552 of the fluorine compound containing propellant fluid 52 leaking from the fluorine compound containing inhaler 32

Figure 5 shows the accumulation step 60 and the transfer step 70 prior to the NMR analysis step 20. The transfer step 70 usually takes place after sufficient time in the accumulation step 60 for the accumulation from any leakage at a predetermined threshold level that still just maintains the container integrity to be reliably detected by the NMR analysis step 20. There may be accumulation losses at the transfer step 70 that have to be compensated by additional accumulation time or increased NMR sensitivity.

Figure 6 shows the pre-evacuation step 30 of the chamber and stabilisation step 110 prior to the cooled accumulation step 100 and a transfer step 90 to a

second container for analysis 80 prior to a second transfer step 70 of the second container into the NMR analysis system for the NMR analysis step 20. The pre-evacuation step 30 may apply to the accumulation chamber or to the second container for analysis or both in order to reduce or eliminate the level of detectable propellant contamination otherwise introduced by the level of room background or by the inhaler leakage prior to the timed accumulation step. Pre-evacuation step 30 may assist faster transport of the leakage into the chamber by reduction of transit time for molecular diffusion across its spaces.

The pre-evacuation step may enhance the level of propellant leakage from the inhaler if it is faulty, for example due to a mal-positioned actuation valve seat or a poor body crimp seal. The pre-evacuation step 30 might well include detection based on chemical detection of gross propellant leaks, so that the control of the inhaler filling, valve crimping and or background levels can be alerted to poor conditions independently of NMR analysis step 20 and also somewhat faster. Peltier or thermo-electric devices do not require the use of cryogenic fluids, thereby providing a convenient cooling means for the test equipment to enhance the NMR signal and or help localise the accumulated propellant. Other cooling means, for example a heat pipe, may also be used to transfer heat from the cooling surface to the Peltier-effect or thermo-electric device. The cooled plate may have absorbants for the propellant in order to help the concentration of the accumulation onto a compact region that is easier to transfer and analyse in another chamber. The stabilisation step 110 between pre-evacuation step 30 and cooled accumulation step 100 is sometimes required to cover transient periods during or immediately after rapid chamber evacuation and also for the proper preparation of the cooled plate forming part of the accumulation chamber wall. The accumulation step 100 may now be longer than before if transfer step 90 has accumulation losses in addition to any losses in transfer step 70.

Figure 7 shows the calibration chamber step 105 and transfer step 65 prior to accumulation step 60 and transfer step 70 into NMR analysis step 20, transfer step 75 and off-line NMR analysis step 25. It is a significant advantage to incorporate a material within or made part of the chamber designed to have material providing an NMR reference signal that can be detected as a means of

proving test equipment sensitivity with every test, which thereby enhances the reliability of the integrity validation. Alternatively, as shown, a known special chamber with material providing such calibration means can be introduced into the NMR analysis system to demonstrate the test equipment sensitivity as required, or regularly, to establish such testing. This can provide a means for cross checking integrity validation with an off-line NMR analysis system. This system can be run in parallel with the normal NMR system for checking product on a batch basis or after a hiatus in the normal production testing. By ensuring that the off-line testing can also handle the accumulated products normally tested by the on-line test system, different measurement periods can be employed in the off-line NMR analysis system in order to establish the actual leakage, surface contamination or room backgrounds with advantage. The provision of a compatible off-line NMR analysis system may provide a significant economic means of increasing throughput or minimising downtime.

Figure 8 shows an embodiment of the test equipment with a cooled endplate 102 forming one wall of the accumulation chamber 6 and also an NMR analysis system 222 having another endplate 101 from an earlier test shown enclosed by lid 78 within tube 441 onto sample well base 442 of magnet 4. Endplate movement means 77 and lid movement means 79 are shown. Standoffs 103 are short spacers providing some thermal barriers for cooled endplates 102 and 101 otherwise in contact with the accumulation chamber 6 and the sample tube 441 through the chamber spacers 68 and sample well base 442 respectively. Flexible coupling means 76 was detached from the endplate movement means 77 and placed with endplate 101 within the second chamber for analysis that has been formed in this embodiment partially inside NMR system 222 by lid 78, tube 441 and sample well 442. After the testing of endplate 101, lid 78 is removed by lid movement means 79 to permit extraction and placement of 101 into another accumulation chamber using another endplate movement means (not shown for clarity). The endplate movement means 77 then places 102 onto 442, decouples from flexible coupling means 76 and then the lid movement means 79 places lid 78 onto tube 441 ready for 222's next NMR testing step.

Figure 9 shows another embodiment of the test equipment where some inhalers 32 are held upside down by means of O-ring type seals 66 within accumulation chambers 6 above endplates 102 mounted by a short flexible coupling means 76 and the endplate cooling, pre-evacuation, accumulation transfer and venting means 130 on small pallets 170 moved by a production line transfer means 150. Spacers 68 and 103 of the accumulation chamber 6 are provided to help retain the inhaler 32 and provide location for the endplate device when the chamber is fully closed up. The accumulation chamber 6 is moved down onto the end plate 102 and makes a close fitting enclosure around the inhaler 32 by means of seals O-ring type seals 67. A reverse of this procedure can be adopted using this equipment for extracting the endplate from the accumulation chamber after the accumulation has been transferred to a second chamber for analysis and the accumulation chamber has been vented through means 130.

Figure 10 shows how the application of NMR test step 21 to an untested inhaler item 3 used to validate or reject an inhaler product by the method or test equipment using NMR results in either a pass NMR test result 23 or a failed NMR test result 24. Failed NMR test result 24 results in the corresponding tested inhaler 34 being consigned to the NMR test reject bin 29. Pass NMR test result 23 results in corresponding tested inhaler 36 being validated as a pass NMR, for example it is then known individually as a "✓NMR" 35 type of product. Alternatively tested inhalers 37 and 36 with pass NMR test results could be marked with a ✓NMR label 39 or be placed into packaging with ✓NMR mark 38. The validation of an inhaler product by any of the methods or test equipment as set out above confers a high level of integrity both for the inhaler and also its production, thereby meeting requirements of the FDA or other regulatory bodies for the demonstration of the required performance of every container used for inhaler products and also for production means of inhaler products. Marking any resultant passed ✓NMR inhaler product itself or even packaging of an inhaler product so validated by the method or equipment conveys an association of high value inhaler products with publicly known MRI techniques and results, justified because the method or equipment used is based on NMR analysis.

As has been described above, testing integrity of a fluid container uses NMR analysis. This is non-destructive and based on physical principles rather than chemical conversion or by signal suppression. It can be applied to testing for leakage of propellant from inhalers containing propellants that are difficult and or expensive to reliably detect directly by other methods. Propellant leakage can be accumulated by condensing on a cooled surface in a pre evacuated chamber to increase the number of propellant molecules or atoms available for detection, usually in proportion to the length of the period used for accumulation, thereby providing a faster analysis for validation by detection of absence of even low-level leakage. Other variations can be envisaged within the scope of the claims.

CLAIMS

1. A method of testing integrity of a fluid container using NMR analysis.

2. The method of claim 1 the fluid container comprising an inhaler, and the testing comprising testing for leakage of propellant from the inhaler.

3. The method of claim 1 or 2 having a step of accumulating leakage in a chamber.

4. The method of claim 1, 2 or 3, the fluid containing fluorine compounds, and the NMR analysis involving detecting fluorine.

5. The method of claim 3 or any claim depending on claim 3, having a step of moving the accumulation chamber into an NMR analysis system.

6. The method of claim 3 or any claim depending on claim 3, having the steps of transferring the accumulation chamber contents into a second container for analysis and then moving this container for analysis into an NMR analysis system.

7. The method of any preceding claim, having the step of carrying out the NMR analysis simultaneously for multiple fluid containers.

8. The method of any of claims 1 to 7 having the step of cooling the leakage.

9. The method of any preceding claim having the step of accumulating leakage on a cooled surface and measuring the amount accumulated.

10. The method of claim 9 having the step of moving the cooled surface relative to an NMR analysis system, to carry out the measurement after a period of accumulation.

11. The method of claim 3 or any claim depending on claim 3, having the step of evacuating the chamber before accumulating.

12. Test equipment having means for validating inhaler integrity using a NMR analysis system for analysis of propellant leakage accumulated within a chamber.

13. The test equipment according to claim 12 where the accumulated propellant leakage has been transferred to another chamber means for introduction into the NMR analysis system for analysis of the leakage.

14. The test equipment according to claim 12 or 13 where the propellant is fluorine containing and the NMR analysis is for 19F nuclei contained within the propellant molecules.

15. The test equipment according to any of claims 12 to 14 having a cooled surface and means for transferring accumulated propellant leakage to the NMR analysis system.

16. The test equipment according to any of claims 12 to 15 having means for pre evacuating the accumulation chamber.

17. The test equipment according to any of claims 12 to 16 whereby the cooling means comprises a Peltier effect device.

18. The test equipment according to any of claims 12 to 17 having means for using a material of the chamber to provide a calibration means for the NMR analysis system.

19. The test equipment according to any of claims 12 to 18 having means for cross checking integrity validation with an off-line NMR analysis system.

20. An inhaler product validated by the method or equipment of any preceding claim.

21. An inhaler product of claim 20 and having a mark to show it has been validated by the method or equipment of any preceding claim.

22. The inhaler product of claim 21, the marking being on packaging of the inhaler product.

ABSTRACT

NMR LEAK TEST

Testing integrity of a fluid container uses NMR analysis. This is non-destructive and based on physical principles rather than chemical conversion or by signal suppression. It can be applied to testing for leakage of propellant from inhalers containing propellants that are difficult and or expensive to reliably detect directly by other methods. Propellant leakage can be accumulated by condensing on a cooled surface in a pre evacuated chamber to increase the number of propellant molecules or atoms available for detection, usually in proportion to the length of the period used for accumulation, thereby providing a faster analysis for validation by detection of absence of even low-level leakage.

(Suggested that Figure 2 accompany the ABSTRACT)

Figure 1

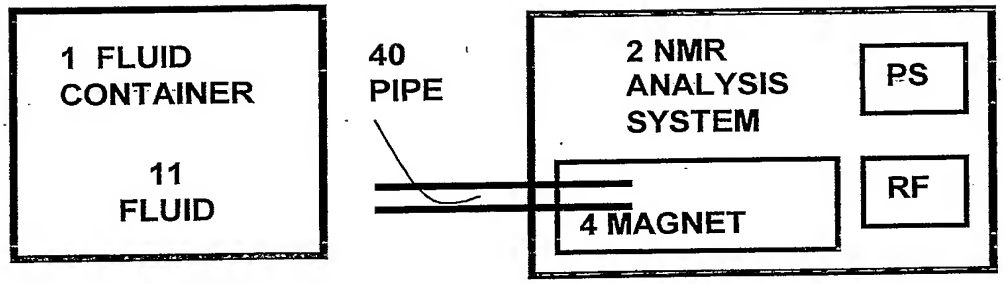


Figure 2

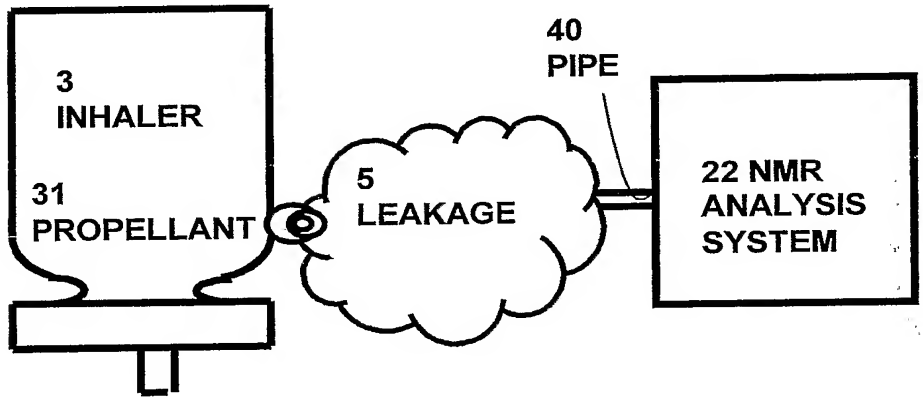


Figure 3

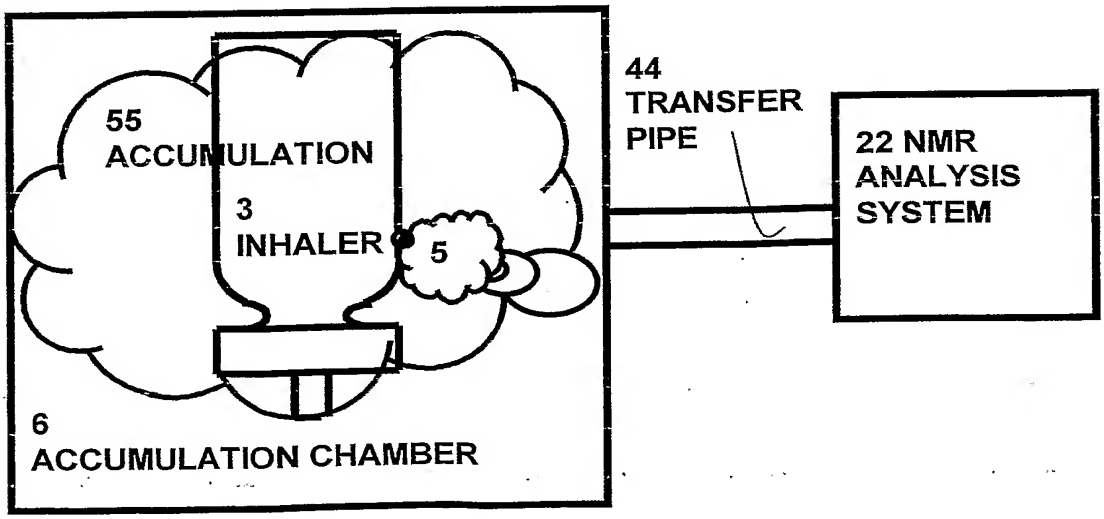


Figure 4

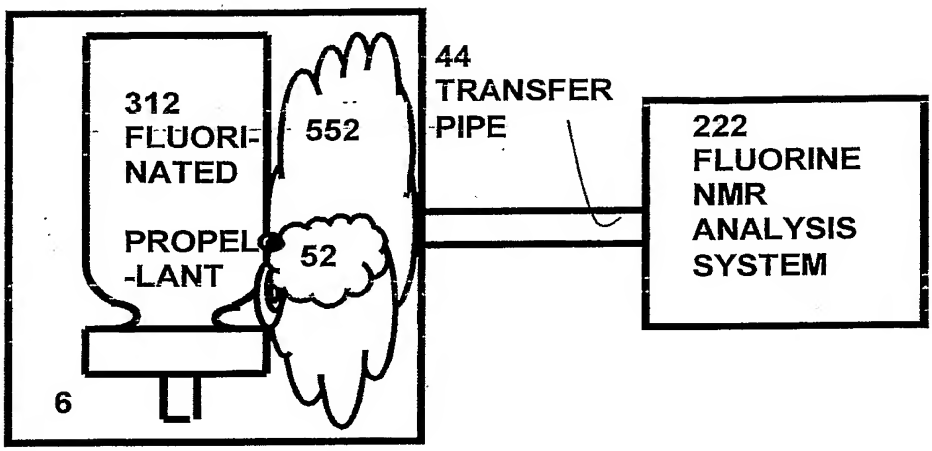


Figure 5

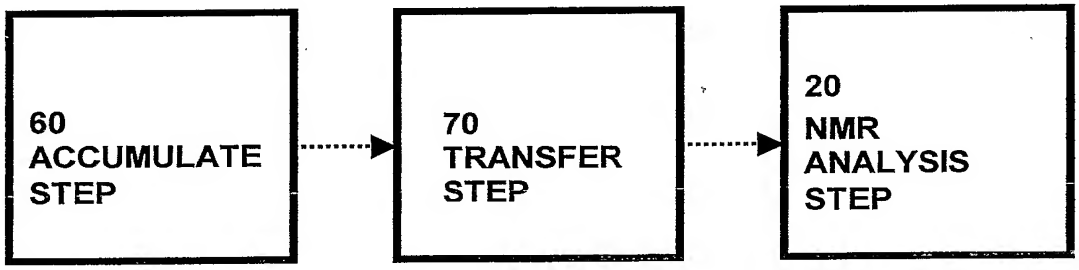
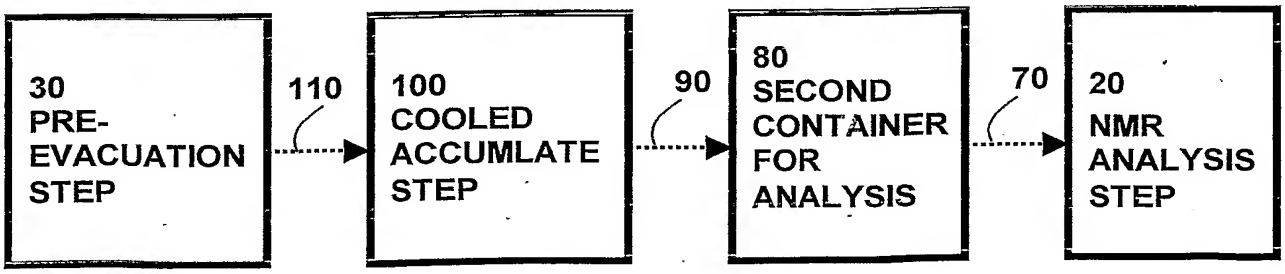


Figure 6



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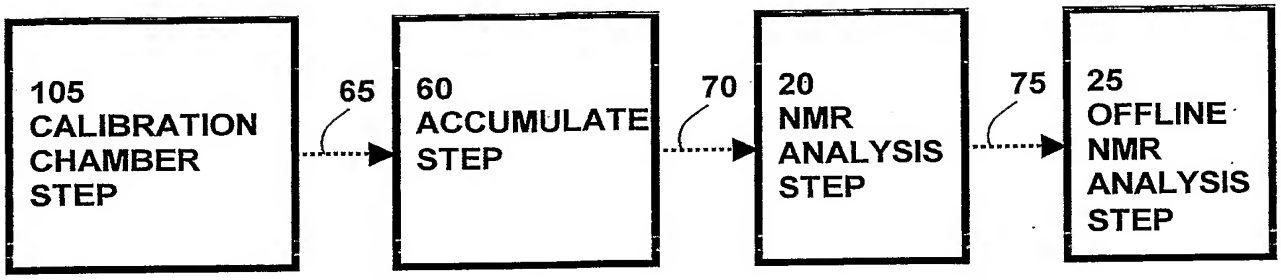

Figure 8

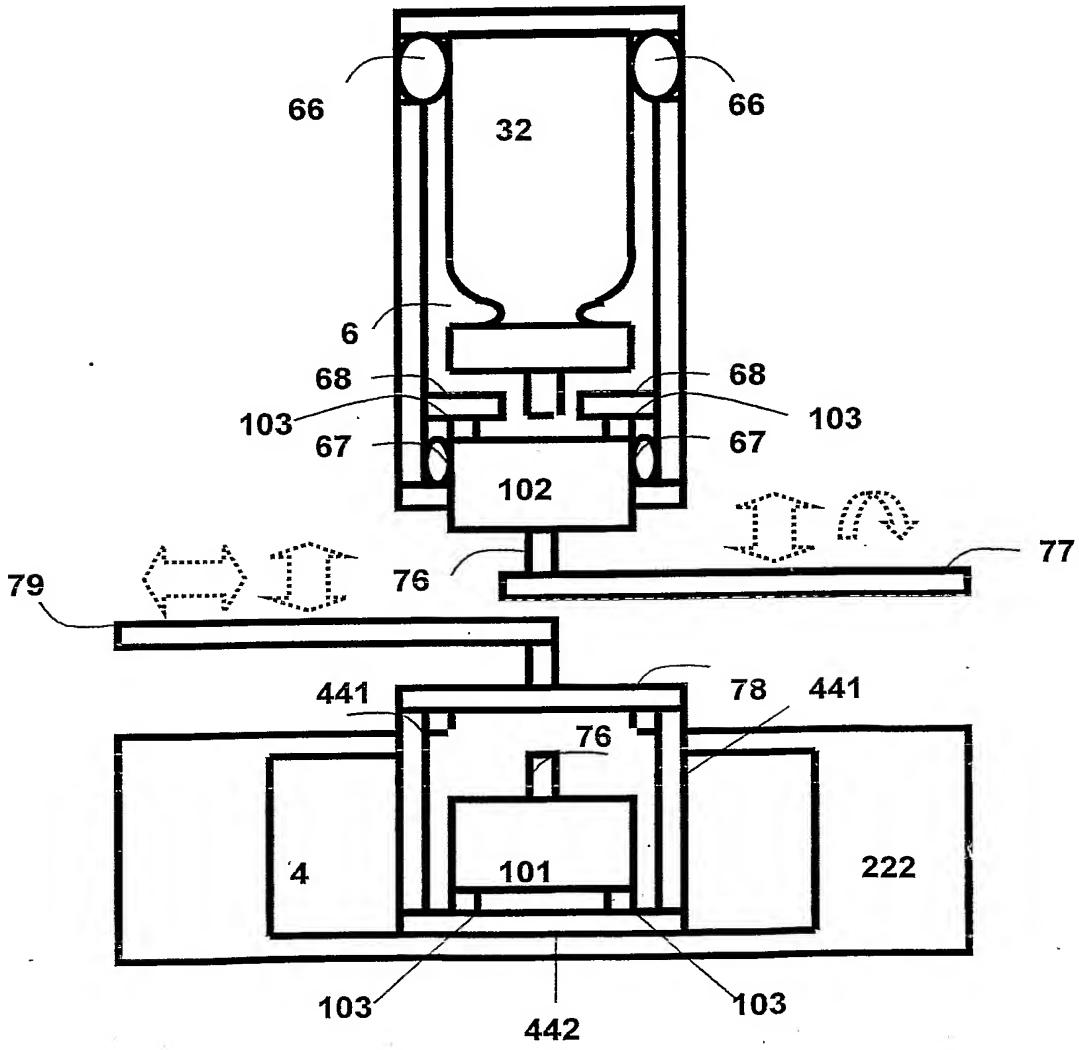

Figure 9

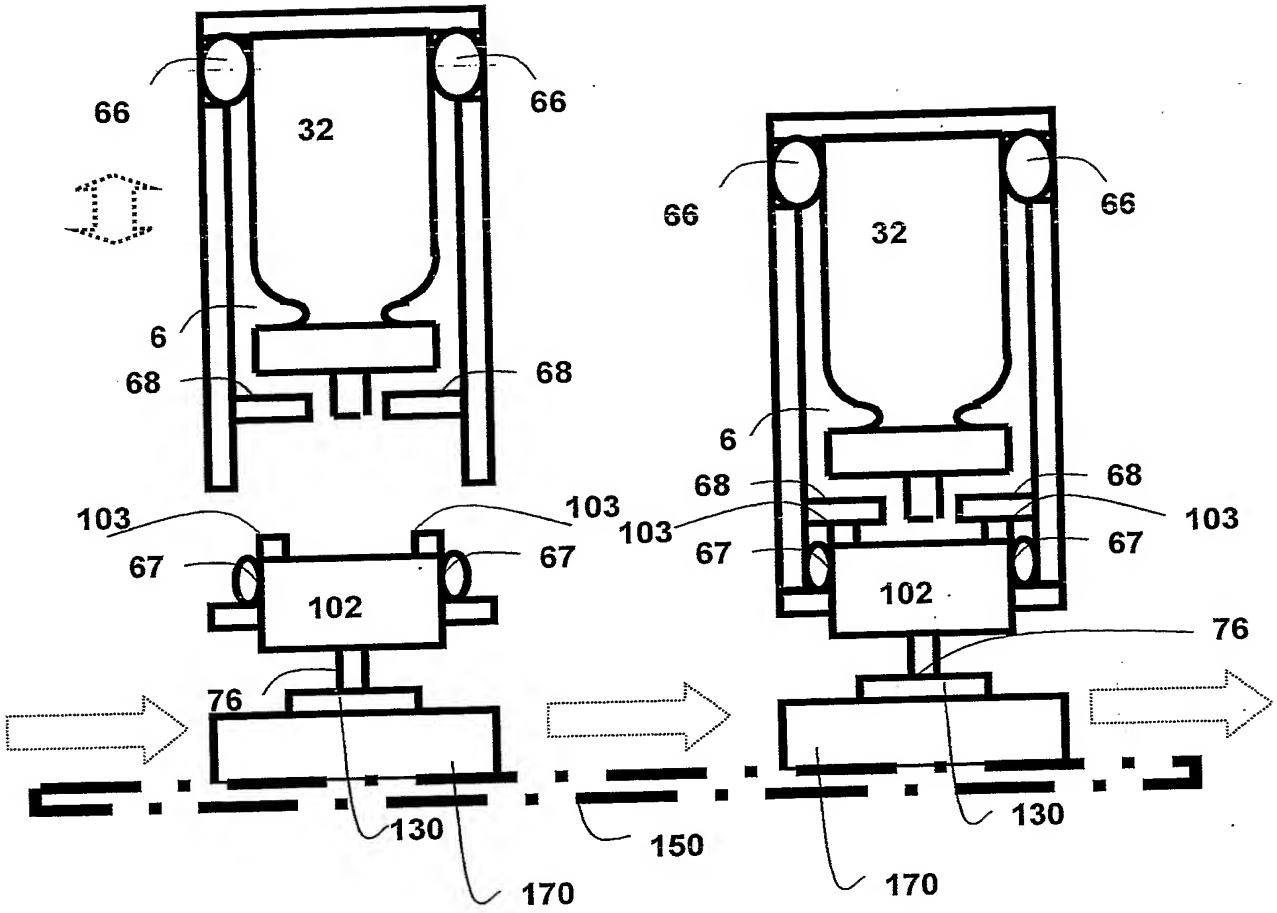
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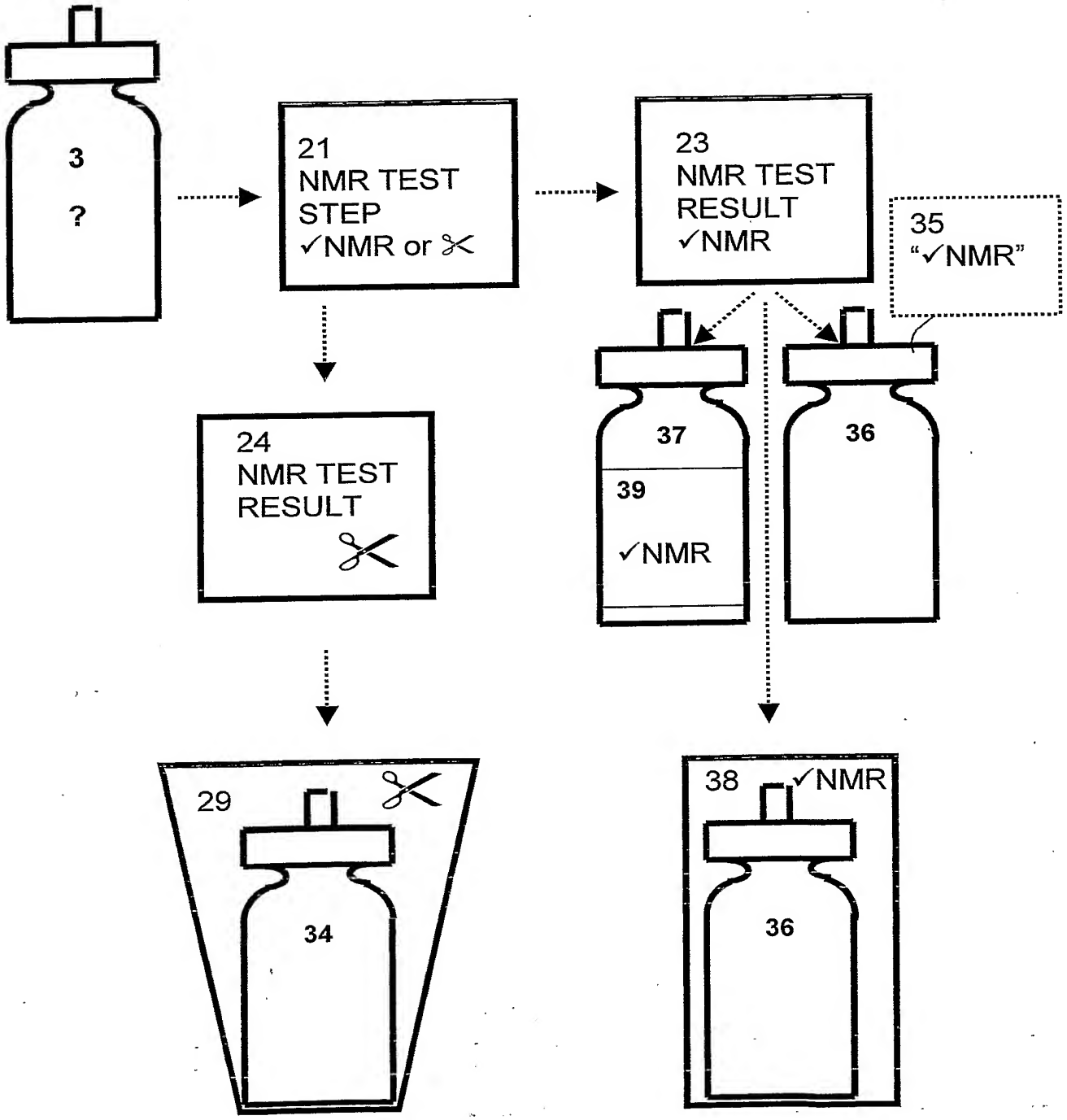
Figure 10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